Twentieth,
January,
1947

Dear Lederberg,

I was very glad to receive your letter, and to have the opportunity of a more leisurely examination of your data.

First of all I checked the agreement of the "coupling" and "repulsion" phases in regard to recombination of T_1 and the marker genes in the sets of data numbered 1, 2 and 3 in your letter. They agree well in 2 and 3 but not so well in 1. Such occasional disagreements are not, however, uncommon in ordinary linkage data and this one should therefore probably not be taken too seriously.

Secondly I checked the agreement of the recombination value for T_1 and the marker genes in sets 1,2, 3 and 4, pooling the coupling and repulsion data from sets 1, 2 and 3. Sets 1 and 3 agree in showing 16.4% and 16.1% recombination, sets 2 and 4 agree with 26.3% and 27.3%. 1 and 3 on the one hand and 2 and 4 on the other clearly disagree. Since 1 and 3 have TP while 2 and 4 have TL (we can exclude B_1 from consideration on the evidence of set 4) we must assume that T_1 is linked to L and P, rather than to T, the difference in recombination being due to the difference in position of L and P. T might of course be in the same chromosome, but it must then be further from T_1 than L and P are. B, M, Ø and C are not brought into this agreement, on the evidence of set 4. This is confirmed by the lack of effect of changing from B, Ø, C to B, M on the recombination value, though it should be noted that if T_1 were chiefly linked with B the same result would be observed.

Dr J. Lederberg ..... Continued..... 20th January, 1947

Data set 4 indicates the order you give, viz.

but we do not know whether this should not really be something like

where reflects not true linkage but the association of two unlinked genes enforced by your technique, which can of course lead to genes in different chromosomes appearing as if in the same branched chromosome. B_1 and Lac would both show linkage with BM and yet appear independent of one another in the data whether the arrangement was or of the kind

This ambiguity can be removed only by separating B and M in the experiments. The recombination value of B_1 with B and M is directly calculable as or about 9%

The recombination values of can be estimated if we care to assume the absence of interference. Setting the recombination values at

we have your four classes $-r_1 -s_1 + v_1 + s$ proportional to $q_1 p_2 q_3$, $q_1 q_2 p_3$, $p_1 q_2 q_3$ and $p_1 p_2 p_3$ respectively $q = 1-p$. We can then find $p_1 = 16\%$, $p_2 = 26\%$ and $p_3 = 16\%$ These add up to 58% but, as you will see, the accuracy of the estimate depends largely on the frequency of the rare + s triple crossover class. I remember that you thought your frequency of 5 for this class to be too high, in which case the values of p_1 --- p_3 would be over-estimated.

As you say, all this depends on the assumption of linear arrangement except, of course, in so far as we recognise the possibility of a branched appearance being spuriously engendered by the technique of insisting that BM etc. be recovered together. Such genes may or may not be linked. Your remark that types such as -++++, +-+++ are rare suggests linkage of B and M etc., but if they all turn out to be linked the result would be somewhat surprising. It may be that linkage of the type we know is not operating in your bacterium, but I think we must at this stage see how far our present ideas of linkage can explain your results.

It also seems to me that the data on strongly suggest a linear order, as the + s class occurs with about the right frequency on such a view. We might expect it otherwise to be higher. A more ordered test of linear order could be made with

(a) 3 linked genes none of which was used as a marker

(b) 2 linked genes also linked to a marker and both "outside" the region between the markers, i.e. not between BM and LT. In this case care must be taken to exclude the possibility of an arrangement such as

which would obviously give a branched appearance.

(c) (I think) 3 gene between the two markers i.e.

Again situation of the types

would have to be excluded.

Possibility (c) requires a bit more examination but I think a linear order could be tested with its aid.

I have not yet had an opportunity to discuss the matter with Fisher, so that all the above is just my own opinion at present. I hope that you find it (a) intelligible, (b) useful and (c) sound. I find the problem a very intriguing one and I hope that I shall see some more of it, or better still, have the opportunity of another personal discussion with you as enjoyable as the one in New Haven. In any case I am sure that you are right in exploring all the possibilities of explaining the results on standard linkage theory as a first step.

Please give my best wishes to Mrs Lederberg. I hope (or should I say, expect ?) that you are both enjoying your new status.

Yours sincerely,

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